Markers of early cardiovascular dysfunction in prehypertension
Prehypertension is associated with higher risk for CV morbidity and mortality

Vasan et al, NEJM, 2001
Prehypertension and cardiovascular morbidity
participants from NHANES I (1971-1975) observed for 18 years for major CVD events; 4,616 HT; 2,708 PHT; 1,662 NT

Low PHT (120-129/80-84 mm Hg) was associated with increased CVD in unadjusted analyses (1.56 [95% CI 1.23-1.98]) but was not statistically significant in adjusted analyses (1.24 [95% CI 0.96-1.59]).

High-normal blood pressure (130-139/85-89 mmHg) remained a predictor of CVD in unadjusted (2.13 [95% CI 1.64-2.76]) and adjusted (1.42 [95% CI 1.09-1.84])

Prehypertension and increased global risk

1968 subjects, general population, no diabetes, no CV events, no therapy
12.8 years follow up

![Graph showing cumulative hazard of composite endpoint](image)

- Hypertension
- High normal blood pressure
- Normal blood pressure
- Optimal blood pressure

Trend: $P = 0.0002$

<table>
<thead>
<tr>
<th>Blood pressure category</th>
<th>Optimal blood pressure</th>
<th>Normal blood pressure</th>
<th>High normal blood pressure</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%total)</td>
<td>624 (32%)</td>
<td>443 (23%)</td>
<td>337 (17%)</td>
<td>564 (29%)</td>
</tr>
<tr>
<td>Observed events (95%CI)</td>
<td>21 (14%)</td>
<td>24 (16%)</td>
<td>32 (21%)</td>
<td>76 (50%)</td>
</tr>
<tr>
<td>Hazard ratios (95%CI)</td>
<td>1</td>
<td>1.2 (0.7–2.1)</td>
<td>$P = 0.56$ 1.8 (1.0–3.1), $P = 0.46$ 2.1 (1.3–3.5), $P = 0.005$</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age and gender.*

*Sehestedt et al. J of Hypertension 2009;27:1165*
Association between prehypertension and chronic kidney disease

7 cohort studies; 261,264 subjects, age range 20-89 years, follow-up 2 to 11 years

Compared to subjects with optimal BP, PHT showed an increased risk of CKD RR = 1.28; 95% CI = 1.13-1.44

women > men

Li et al. PloS One 11(6):e0156575
Prehypertension - highly prevalent entity
Prehypertension in Croatian general population
EH-UH study

- **optimal**
  - **f**: 14.9
  - **m**: 25.4

- **normal**
  - **f**: 16.8
  - **m**: 22.1

- **high normal**
  - **f**: 20.2
  - **m**: 25.4

- **stage 1**
  - **f**: 11.3
  - **m**: 12.7

- **stage 2**
  - **f**: 8.2
  - **m**: 7.9

- **stage 3**
  - **f**: 2.5
  - **m**: 2.8

- **ISH**
  - **f**: 15.3
  - **m**: 13.9

37% women
47.5% men

Jelaković et al. Unpublished data
Prehypertension - highly prevalent entity

Prehypertension – heterogeneous entity

- Men vs. Women; Younger vs. Older

- Metabolic disturbances; Renal impairment

- Race dependent (white – neurogenic; black – salt sensitivity – volume expansion)
PHT is a heterogeneous group subjects with PHT differ in mechanisms, pathways and natural history.

Figure 1. Associated risk factors, general mechanisms, early cardiovascular dysfunction and natural history in prehypertension

scientific interest but also of utmost pragmatical importance to identify PHT individuals with higher CV risk who are more likely to progress and who will mostly benefit from early interventions.

For risk classification it is important to determine presence of different associated risk factors which cluster in PHT, to detect presence of subclinical target organ damages and early CV dysfunction.
Markers of Early Cardiovascular Dysfunction in PHT

- Endothelial dysfunction and albuminuria
- Retinal changes
- Arterial stiffness
- Carotid Intima Media Thickness
- Changes of left ventricular structure and geometry
- Left ventricular diastolic function
- Left ventricular systolic function
**Endothelial dysfunction in PHT**

Weil et al. - significantly lower forearm blood flow responses to acetycholin (~30%) in PHT compared with NT

-> PHT is associated with impaired NO-mediated endothelium-dependent vasodilation

Nikolov et al. - flow-mediated-dilatation was reduced in PHT compared to NT group which was associated with increased ADMA and cVCAM-1

Wang et al. - association of elevated CRP and sICAM-1 with PHT

-> inflammation and endothelial dysfunction may have a role in the development of PHT and HT

Albuminuria as a mirror and reflection of endothelial damage
Albuminuria as an early biomarker in PHT

Prevalence of MA in general population

Some authors failed to find MA in PHT subjects, -> this was explained with younger age of subjects enrolled in those studies

High normal BP – independently significant association with MA
OR 1.69, 95%CI 1.09-2.61
Significant association between glycemic level and MA was present in PHT but not in OBP group
Microalbuminuria in non-diabetic prehypertensive subjects

Prehypertension is a risk for development of microalbuminuria in general population

2338 nonalbuminuric subjects, follow-up 2.4 years

Cumulative incidence of MA according to baseline BP

High-normal DBP, triglyceride, FBG – significant predictors of MA

Konno et al, J of Hypertension 2013;31:798
Albuminuria as a predictor of outcome in prehypertension

1968 subjects, general population, no diabetes, no CV events, no therapy
12.8 years follow up

10 year event rate
3.0%

10 year event rate
12.1%

10 year event rate
24.9%

Measuring two of ACR, PWV or atherosclerotic plaques improves risk prediction

Sehestedt et al. J of Hypertension 2009;27:1165
Prehypertension is associated with numerous cardiovascular risk factors
Croatian BP Rural Study
(n= 1289)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Optimal BP</th>
<th>Prehypertension -&gt; high normal BP</th>
<th>Hypertension -&gt; stage 1 untreated</th>
<th>*p</th>
</tr>
</thead>
<tbody>
<tr>
<td>36.93±18.5</td>
<td>&lt; 44.98±14.25</td>
<td>55.58±14.72</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>4.64±0.53</td>
<td>&lt; 4.95±0.63</td>
<td>5.66±1.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.11±1.12</td>
<td>&lt; 5.49±1.12</td>
<td>6.03±1.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.52±0.35</td>
<td>1.54±0.37</td>
<td>1.60±0.42</td>
<td>0.363</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.05±0.93</td>
<td>&lt; 3.33±0.94</td>
<td>3.72±1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ratio HDL/LDL</td>
<td>0.53±0.161</td>
<td>0.51±0.24</td>
<td>0.48±0.31</td>
<td>0.107</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.24±0.96</td>
<td>&lt; 1.36±0.78</td>
<td>1.74±1.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.66±4.08</td>
<td>&lt; 26.36±4.35</td>
<td>28.09±5.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>85.99±10.25</td>
<td>&lt; 91.67±11.13</td>
<td>97.87±12.69</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Jelaković et al unpublished data
Renal function of prehypertensives

Renal impairment is present in PHT – cause or consequence?

Proximal tubule damage – early sign?

Jelaković et al unpublished data
Younger vs. older prehypertensives - differences in renal impairment

Younger, but not older PHT have proximal tubule damage

Jelaković et al unpublished data
Albuminuria as an early biomarker in PHT

PHT (particularly high-normal BP) are significantly associated with increased MA

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES III</td>
<td>2.13</td>
</tr>
<tr>
<td>Kim et al</td>
<td>1.69</td>
</tr>
<tr>
<td>Peng et al</td>
<td>1.83</td>
</tr>
</tbody>
</table>

PHT subjects with MA had higher GFR levels than those with normoalbuminuria

-> PHT might cause endothelial dysfunction and glomerular hypertension inducing glomerular hyperfiltration

Prehypertension and glomerular hyperfiltration – risk for renal impairment?

Non-treated subjects without diabetes and CKD

Prevalence of glomerular hyperfiltration

Jelaković A, ESH Paris 2016, oral presentation
1. Prevalence of MA is higher in PHT than in subjects with OBP, but lower than in non-treated HT.

2. Subjects with PHT have higher risk for MA than those with normal BP.

3. Association of MA with PHT is present in diabetics but also in non-diabetics.

4. Negative results were observed in children and adolescents what could be explained with shorter period of exposition to higher values of BP.

MA might be considered as a tool for identification of adult and elderly PHT subjects (with additional high risk) who may benefit from early treatment.
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MA might be considered as a tool for identification of adult and elderly PHT subjects (with additional high risk) who may benefit from early treatment.
Retinal changes as an early marker in PHT
new techniques and technologies in retinal photography have enabled investigations of microvascular structure and function in retina.

- NT subjects with retinal arteriolar narrowing were more likely to develop HT
- the central retinal arteriolar equivalent (CRAE) was equivalent to those of the hypertensives and significantly lower than those of NT group

- the recent study in HT and PHT adolescents has shown negative correlation between CRAE and both periferal (brachial) and central SBP.

- in young adults and of small children high BP had no influence on retinal venular diameter.

- The plausable explanation of these findings could be the short cumulative exposure of the children and adolescents to high BP

Structural alterations of the retinal microcirculation in prehypertension

arteriolar-venular ratio in PHT was below the normal values i.e. greater than 0.92, indicating occurrence of an initial arteriolar narrowing process in the high-normal BP group

-> retinal arteriolar narrowing is an early phenomenon in PHT, and systolic BP and PP represent the major haemodynamic determinants of the retinal abnormalities in PHT

Retinal changes as an early marker in PHT

1. There is scarce evidence on retinal changes in PHT.

2. It was reported that systolic BP and PP in PHT represent the major haemodynamic determinants of the retinal abnormalities i.e. arteriolar narrowing.

3. Negative correlation of retinal changes with BP was found in PHT adolescents and these findings could be due to the short cumulative exposure of the children and adolescents to high BP.

Retinal changes in PHT might be considered as an early sign in adults, but further studies are needed.
Arterial stiffness as an early marker in PHT

Increased arterial stiffness was observed already in PHT adolescents and children. Stabouli et al. reported in the study of 124 children and adolescents 5 to 18 years of age that 24-h ABPM, daytime and nighttime PP levels were significantly higher in PHT and HT than in NT subjects. Urbina et al. reported a graded increase in carotid-femoral PWV from NT to PHT and to HT youth aged 10-23 years (5.75 vs. 6.38 vs. 7.12 m/s) after adjusting for other CV risk factors. Lurbe et al. found similar gradual increase in PWV in HT, PHT (high normal BP) and HT in a group of children aged 8 to 18 years. It was proposed that increased AS in children with high BP in the early stage could be explained by passive distension caused by arterial pressure and not primarily with intrinsic arterial wall changes. Phillips et al. Appl Physiol Nutr Metab. 2015; 40(1):72; Stabouli et al. Pediatr Nephrol. 2009; 24(8):1545 et al.; Garcia-Espinosa et al. Pediatr Cardiol. 2016; 37:1340; Urbina et al. J Clin Hypertens (Greenwich). 2011; 13:332; Lurbe et al.. Hypertension. 2012; 60:550-5.
PWV is higher in subjects with prehypertension than in those with normal BP

2,619 Japanese (mean age 44±9 years); 984 normal BP, 1349 PHT and 286 HT

Even after adjustments for confounding variables (age, gender, and mean BP), PWV was higher in subjects with PHT than in those with normal BP

-> the CV risk related to AS may be increased in subjects with PHT as compared with that in subjects with normal BP

Prehypertension, pulse pressure and mortality

3,632 subjects, (age range, 25–64 years); mean follow-up, 15.2 years
PHT prevalence 21.6%, no diabetes, no CV events
San Antonio Heart Study

<table>
<thead>
<tr>
<th>Prehypertension (SBP 120–139 mm Hg and/or DBP 80–89 mm Hg)</th>
<th>Lower tertile of pulse pressure (≤37 mm Hg)</th>
<th>8/134</th>
<th>1.19 (0.52–2.73)</th>
<th>2/130</th>
<th>0.43 (0.05–3.40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle tertile of pulse pressure (38–45 mm Hg)</td>
<td>18/258</td>
<td>1.83 (1.02–3.29)</td>
<td>4/257</td>
<td>1.24 (0.38–4.06)</td>
<td></td>
</tr>
<tr>
<td>Upper tertile of pulse pressure (≥46 mm Hg)</td>
<td>79/756</td>
<td>2.14 (1.38–3.32)</td>
<td>33/745</td>
<td>2.47 (1.13–5.39)</td>
<td></td>
</tr>
</tbody>
</table>

\(P_{\text{for trend}} = 0.16\)

PHT is an independent predictor of all-cause and CV mortality in subjects free of diabetes and CV disease, but only if PP was widened

-> PHT is not a risk factor for mortality if PP was narrow.

It was proposed that widened PP may select a group of individuals who are more susceptible to generalized vascular damage and atherosclerosis

Arterial stiffness as an early marker in PHT

Gradual increase in arterial stiffness was observed from NT to PHT and HT.

Further research is needed to clarify the chicken-egg question whether increased arterial stiffness is risk factor for PHT, or does PHT independently increases arterial stiffness.

Measurements of biomarkers of arterial stiffness (PP, carotid-femoral PWV etc.) are valuable in identification PHT subjects with higher CV risk.
Prehypertension and carotid Intima-Media Thickness

Urbina et al. presented an increased cIMT in PHT children and adolescents compared to the NT as independent determinant of target organ damage (TOD). Jourdan et al. reported thicker carotid and femoral IMT in young people who had systolic BP in the top 10th percentile of the distribution. Stabouli et al. reported that obese children and adolescents have greater cIMT than nonobese subjects, independently of BP. During childhood and adolescence, cIMT correlates with age and with the increase in BP. Urbina et al. (J Clin Hypertens (Greenwich). 2011;13:332); Jourdan et al. (J Hypertension. 2005;23:1707); Stabouli et al. (Hellenic J Cardiol. 2012;53:41). Manios et al. (Atherosclerosis 2011;214:215).
In PHT cIMT is increased independently of BP and known determinants of wall thickness.

Prehypertension and carotid Intima-Media Thickness

1931 subjects, 136 PHT; age 55 years; 3.5 years follow up

The Mexico City Diabetes Study

Prehypertension is associated with increased cIMT and carotid atherosclerotic plaque

942 subjects, 309 PHT; age range 46 to 75 years

Determinants of thicker cIMT and plaque formation

- **PHT**: 1.65 (0.97, 2.82) \( p = 0.067 \)
  - 2.36 (1.43, 3.88) \( p = 0.001 \)
- **HT**: 2.33 (1.40, 3.87) \( p = 0.001 \)
  - 1.88 (1.15, 3.07) \( p = 0.012 \)

PHT - trend to have thicker carotid IMT
- plaque formation as significant as that in hypertension.

Hong et al. BMC Cardiovascular Disorders 2013;13:20
Prehypertension and Common Carotid Artery Intima-Media Thickness and LVM

896 subjects, 212 PHT; mean age 51+/−16

PHT - higher cIMT and LVM than NT counterparts.

-> PHT is cross-sectionally associated with subclinical atherosclerosis and TOD

Manios et al. Stroke 2009;40:1515
Prehypertension and carotid Intima-Media Thickness

1. Most of studies showed an independent positive association between PHT and cIMT starting from childhood and adolescence till the older ages.

2. In PHT other risk factors (i.e. dyslipidemia, morning BP surge, masked HT) additionally increase risk for thicker cIMT.

3. Presence of cIMT is associated with other target organ damages (i.e. LVH)

4. In addition to the presence of thicker cIMT it was also reported that intensity of atherosclerotic plaque formation in PHT is not different to HT.

Thicker cIMT is reported to be associated with PHT and could be considered as a determinant of early target organ damage.
Changes of LV structure and geometry as an early sign of CV dysfunction in PHT

Changes in LV structure and geometry are registered already in children and adolescents with PHT as well as higher and LVM.

Stabouli et al. reported the same prevalence of LVH of 20% in HT and PHT children.
PHT children had higher LVMI than NT and similar to HT.

Falkner et al. found that the combination of obesity and PHT increases the likelihood of LVH (19% and 57% in normal weight and overweight adolescents).

Urbina et al. failed to find difference in concentric HT between PHT vs. NT while eccentric hypertrophy was slightly more prevalent (4.6% vs. 3.4%).

Drukteinis et al. in the Strong study revealed in young PHT (14-39 years of age) that after adjustment for covariates, both HT and PHT subjects had higher LV wall thickness (0.83 and 0.78 versus 0.72 cm), LVM (182 and 161 versus 137 g), and RWT (0.30 and 0.29 versus 0.28 cm).

References:
- McNiece et al. Hypertension. 2007; 50:392
- Vettore Zanetti Zilla, In laguna
Prehypertension and left ventricular mass

Abnormal LV geometry by categories of hypertension status

Abnormal geometry was defined as presence of concentric remodeling, concentric or eccentric hypertrophy.

35086 NT; 9283 PHT; 4795 HT

Changes of LV structure and geometry as an early sign of CV dysfunction in PHT

1. Left ventricular mass is higher in PHT than in NT counterparts.

2. Changes in LV structure and geometry are presented already in PTH children and adolescents.

3. PHT subjects displayed more pronounced aging-related changes in LV structure than NT.

4. Some authors argued that associated risk factors and not PHT itself are principally responsible for LV structural changes.

Regardless changes in LV structure are independently related to PHT or they are associated with other risk factors.

Observed abnormalities in structure and geometry in PHT are similar to those in newly diagnosed, untreated HT patients, although in a milder manner.
Jung et al found the adjusted mean E/E ratio, indicating increased filling pressure was 7.89 (95% CI 7.85 - 7.94) in PHT who also had higher E/e ratio, LA diameter, while lower E/A ratio and septal e velocities.

Bajpai et al. observed active (E) and passive (A) transmitral peak velocities and their ratio (E/A ratio) to be decreased in PHT what is suggestive of compensatory diastolic dysfunction.

Ahn et al. reported that diastolic function was more decreased in PHT compared to NT (E/A men 1.14 (0.6) vs. 1.3 (0.4); women 1.11 (0.6) vs. 1.25 (0.5)).

Celik et al. found that PHT compared to NT had slower E velocity, faster A velocity, lower E/A ratio, longer deceleration time and IVRT (isolometric relaxation time).

Kim et al. found that LV diastolic parameters (using TDI) E/E ratio, TDI Ea velocity, E/Es ratio were impaired in PHT subjects.
Left ventricle diastolic function in general population

NT 35086; PHT 9283; New HT 1818

Young Jung et al. Hypertension Research 2017;40:606
Left ventricular diastolic dysfunction and PHT

It is interesting to analyze changes in LV function in various ageing PHT subgroups.
Prehypertension and left ventricular diastolic dysfunction

Adolescence and young adults
N= 1940; age 14-39

Middle-aged adults
N=1792; age 48-58

Elderly
N=537; age 61-71

Diastolic dysfunction by categories of BP status

Left ventricular diastolic dysfunction and PHT

142 NT; 119 PHT, 39 years of age; 10-year follow up period

The ratio of early and late diastolic peak transmitral flow velocities (E/A) decreased by 15.7% (compared to decrease of 7.7% in NT).

The ratio of early diastolic peak myocardial relaxation velocities (E/EM) was higher and LA size was larger in PHT group.

The adjusted OR for incident diastolic dysfunction was 2.52 (1.01-6.31) for the PHT group.

Markus et al J of Hypertension 2008, 26:2040
Left ventricular diastolic dysfunction and PHT

1. Diastolic function is more decreased in PHT than in NT, but not so severely as it was described in HT.

2. Impaired diastolic function is present not only in middle-aged and elderly PHT, but also in young PHT and even in children and adolescents indicating that this is one of the earliest manifestation of cardiovascular dysfunction in PHT.

3. In subjects with PHT compared to NT diastolic function decreased more rapidly.

4. Although majority of authors found PHT to be independently associated with diastolic dysfunction, some authors suggested that observed changes are more likely attributed to associated risk factors which cluster with PHT.

Left ventricular diastolic dysfunction is an early and prominent sign of cardiovascular dysfunction in PHT.
Left ventricular systolic function in PHT

Even in elderly PHT authors failed to find differences in LV systolic function in PHT compared to subjects with OBP. In the elderly PHT enrolled in the ARIC study neither EF nor circumferential strain significantly differed between NT and HT, and authors speculated that systolic abnormalities restricted to the subendocardial fibers might be present only in a more advanced HT status.

In the Korean Genome study no statistically significant differences in LV systolic parameters, including EF and TDI systolic (Sa) velocity were observed between PHT and NT.

Drukteinis et al. found that circumferential end-systolic stress was significantly elevated in both young-to-middle-aged HT and PHT compared to NT, but the circumferential end-systolic stress/end-systolic volume index, a load-adjusted measure of chamber contractility, did not differ among groups after adjustment.

Contrary to LV diastolic dysfunction the overall LV systolic functions were reported to be normal in asymptomatic PHT subjects.


Emanuel Vidović, Della laguna veneta
Prehypertension is not associated with left ventricle systolic dysfunction

1940 subjects, 14 to 39 years, ECHO
The Strong Heart Study

1229 NT, 442 PHT
53 years of age, ECHO plus Tissue Doppler
Korean Genome Study

402 NT, 537 PHT, 3932 HT;
66 years of age, 2-D ECHO
ARIC Study

Prehypertension display more pronounced ageing-related increase in LV mass and raised incidence of LVH and LV concentric remodeling

The MONICA/KORA Augsburg study

1005 subjects; 295 PHT, 114 PHT followed up for 10 years

PHT was associated with a raised incidence of LV concentric remodeling (adjusted OR 10.7 (CI 95% 2.82-40.4)) and LVH (adjusted OR 5.3 CI 95% 1.58-17.9)

contrary to diastolic function, systolic function did not display any substantial changes

-> this may indicate that persistent PHT does not affect contractility

-> in 10 year follow up persistent PHT accelerates the development of hypertrophy and diastolic dysfunction.
1. In PHT there are even fewer data on LV systolic function than on diastolic dysfunction.

2. Using routine ECHO techniques LV systolic functions were reported by most of authors to be normal in asymptomatic PHT subjects. It was observed even in elderly PHT subjects.

3. Interestingly, using more sophisticated methods (2D strain ECHO, MRI) early changes in systolic dysfunction were found.

4. Some authors raised the question whether PHT itself, i.e. BP values or metabolic abnormalities associated with PHT were significantly related to the reduction of LV systolic function in PHT.

Results on LV systolic dysfunction in PHT are controversial.

More sophisticated techniques found early systolic dysfunction but the question whether this is independently related to PHT or is influenced with clustered metabolic abnormalities is still opened.
<table>
<thead>
<tr>
<th>Early CVD markers</th>
<th>Children and adolescents</th>
<th>Adults and elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial dysfunction</td>
<td>No data</td>
<td>Positive</td>
</tr>
<tr>
<td>Retinal changes</td>
<td>No association/negative</td>
<td>Positive Blood pressure</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Negative</td>
<td>Positive Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ associated clustered risk factors (glycemia, uric acid, obesity)</td>
</tr>
<tr>
<td>Arterial stiffness</td>
<td>Positive Blood pressure</td>
<td>Positive Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ associated clustered risk factors (age, dyslipidemia)</td>
</tr>
<tr>
<td>Carotid intima-media-thickness</td>
<td>Positive Blood pressure</td>
<td>Positive Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ obesity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ associated clustered risk factors (men, dyslipidemia, morning BP surge)</td>
</tr>
<tr>
<td>Left ventricle structure and geometry</td>
<td>Positive Blood pressure</td>
<td>Positive Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ obesity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ associated clustered risk factors (insulin resistance)</td>
</tr>
<tr>
<td>Left ventricle diastolic dysfunction</td>
<td>Positive Blood pressure</td>
<td>Positive Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ associated clustered risk factors</td>
</tr>
<tr>
<td>Left ventricle systolic dysfunction</td>
<td>No association</td>
<td>Negative/positive* Blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ metabolic abnormalities</td>
</tr>
</tbody>
</table>
## Proposed diagnostic tests for detection early CV dysfunction

<table>
<thead>
<tr>
<th>Children and adolescents</th>
<th>Adults and elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>Pulse wave velocity</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>Ambulatory BP monitoring</td>
<td>Ambulatory BP monitoring</td>
</tr>
<tr>
<td>Left ventricle ultrasound</td>
<td>Left ventricle ultrasound</td>
</tr>
<tr>
<td>Carotid intima-media thickness</td>
<td>Carotid intima-media thickness</td>
</tr>
<tr>
<td>Optic fundus photography</td>
<td>Optic fundus photography</td>
</tr>
</tbody>
</table>
The aim of science is not to open a door to endless wisdom, but to put a limit to endless error.

Bertold Brecht, The Life of Galileo